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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/452,843	05/30/95	SETTE	A 014137-00802

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EXAMINER	
DIBRINO,M	
ART UNIT	**PAPER NUMBER**
1644	29

DATE MAILED: 10/25/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applic...
08/452,843	Sette et al
Examiner	**Group Art Unit**
Marianne DiBrino	1644

☒ Responsive to communication(s) filed on Jan 28, 2000

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 67-165 is/are pending in the applicat

Of the above, claim(s) 76, 77, 86-88, 91, 93-100, 117-119, 122, 124-131, 140, 141, 155, 156 is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 67-75, 78-85, 89, 90, 92, 101-116, 120, 121, 123, 132-139, 142-154, and 157-165 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). #23, filed 8/20/99

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant is required to provide SEQ ID NO for the sequences listed in the Figures. Applicant is further required to list priority data in section (1)(vii).

2. Applicants are required to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, Figures 1 and 2). 37 CFR 1.821(d).

3. Applicants' responses filed 1/28/00, 7/20/00 and the amendments filed 7/22/99, 8/20/99 and 6/13/00 are acknowledged and have been entered.

Claims 67-165 are pending.

4. Applicants' election with traverse in Paper No. 18, filed 6/13/00, of the Invention of Group I (claims 67-75, 78-85, 89-116, 120-139, 142-154 and 157-165) and the species of peptide APAPAPSWPL, which is SEQ ID NO: 14, the species of cancer associated antigen p53 and the species of HLA molecule HLA-B0701 is acknowledged. The traversal is for the reasons of record in Paper No. 26 (filed 3/28/00) and Paper No. 28 (filed 7/20/00).

5. In view of Examiner's meeting with BPS Richard Schwartz on 7/26/00 and Applicant's traversal, the Examiner has modified the election in the instant application to require the election of one ultimately disclosed species of peptide, i.e., a specific SEQ ID NO, and one ultimately disclosed species of antigen of interest, and to eliminate the requirement for the species of "motif" as well as for the species enunciated in items # 7, 9 and 10 of the Restriction Requirement mailed 11/24/99 (Paper No. 24). Therefore, Applicants' election, as detailed in item #2 of this Action supra, fulfills the Restriction Requirement made by the Examiner.

Claims 67-75, 78-85, 89, 90, 92, 101-116, 120, 121, 123, 132-139, 142-154 and 157-165 read on the elected species, SEQ ID NO: 14, cancer associated antigen p53 and HLA-B0701, and are currently being examined.

Claims 76, 77, 86-88, 117-119, 140, 141, 155, 156 (non-elected Group II) and claims 91, 93-100, 122 and 124-131 (non-elected species of Group I) are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claims 67-75, 78-85, 89, 90, 92, 101-116, 120, 121, 123, 132-139, 142-154 and 157-165 are currently being examined.

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: a post office address was not provided for the second inventor.

7. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 67-75, 78-85, 89, 90, 92, 101-116, 120, 121, 123, 132-139, 142-154 and 157-165 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

This rejection is a new matter rejection.

The added material which is not supported by the original disclosure is as follows:

(1) an "epitope consisting of about 8-11 residues that comprises an HLA B7 supermotif". The instant specification discloses on page 3 at lines 5-6 "The oligopeptides of the invention...usually consist of between about 8 and about 11 residues". Applicants point to page 3, lines 19-21 and lines 5-7 for support for an "epitope consisting of about 8-11 residues", however, the specification discloses that "motif" refers to the pattern of residues in a peptide of defined length, usually about 8 to about 11 amino acids, which is recognized by a particular MHC allele. " There is no disclosure of an "epitope consisting of about 8-11 residues which comprises an HLA B7 supermotif".

(2) "HLA B7 supermotif" or "HLA structural supermotif". The instant specification discloses on page 3 at lines 22-23 the term "supermotif" and on page 4 at lines 22-25 the term "B7-like-supermotifs", but the instant specification does not disclose the term "HLA B7 supermotif".

(3) "epitope consists of about 8-11 amino acid residues and is identified by the presence of an HLA-B7 structural supermotif associated with peptide binding to multiple HLA molecules, said structural supermotif comprising a first amino acid anchor residue at position two from the

epitope's N-terminal residue, said first anchor residue selected from the group consisting of P and a second anchor residue selected from the group consisting of V, I, L, F, M, W, Y and A as the epitope's carboxyl-terminal amino acid residue". The instant specification discloses formulae on page 4 at lines 19-25 that indicate that "supermotifs" or "B7-like-supermotifs" are characterized as 9 or 10-mer peptides with P at position 2 and A, V, I, L, M, F, W or Y at the carboxy terminus. There is no disclosure of 8 or 11-mer peptides with P at position 2 and A, V, I, L, M, F, W or Y at the carboxy terminus.

(4) "isolation of the one or more peptide fragments from a natural source". The specification provides no disclosure of said phrase.

(5) "proviso that the immunogenic peptide does not comprises an entire native antigen". Applicants point to support in the specification on page 3 at line 28 through page 4 at line 2. However, the specification at these locations disclose "the peptides of this invention do not contain materials normally associated with their in situ environment, e.g., MHC molecules on antigen presenting cells."

(7) a peptide or peptide fragment thereof which comprises an IC50 of less than about, 50nM or 125 nM for an HLA molecule. Applicants point to the specification of parent application 08/344,824, incorporated by reference, on page 57, Table 14 for support. Although some of the peptides listed in Table 14 have an IC50 of less than 50nM or an IC50 of less than 125 nM, there is no disclosure in the instant specification of an IC50 of less than about 50nM or of less than 125 nM for the invention as broadly claimed.

(8) "a peptide fragment of more than about 11 amino acid residues in length." Applicants point to the specification on page 12 at line 32 through page 13, at line 4 and page 13 at lines 26-27; however, there is no such disclosure.

(9) "HLA-Cw6 molecules". The specification of parent application 08/344,824, incorporated by reference, discloses only two species of HLA-Cw6 molecules, namely, HLA-Cw0602 (Table 6, page 33) and Cw0601 (Table 3, page 10) and the parent application 08/278,634 only discloses HLA-Cw3.

(10) "a method for using a peptide in accordance with" "a method for making an immunogenic peptide", for example, such as recited in claims 113 and 84, respectively or in claims 137 and 115, respectively, or in claims 150 and 139, respectively (e.g., because it reads on a method of making and using a peptide while there is no disclosure of such a hybrid method in the instant specification).

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 67-75, 78-85, 89, 90, 92, 101-116, 120, 121, 123, 132-139, 142-151 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 73, 143 and 161 are indefinite in the recitation of "natural source" because it is not clear what is meant.

b. Claims 113, 114, 137, 138, 150 and 151 are indefinite in the recitation of " A method *for using* a peptide fragment in accordance with claim" 84, 113, 115 and 138, respectively, because base claim 84 from which said claims 113, 114, 137 and 138 ultimately depend is a method *for making* an immunogenic peptide and because base claim 139 from which said claims 150 and 151 ultimately depend is a method for selecting a peptide. There is lack of antecedent basis for said limitation.

c. Claims 67, 80, 84, 115, 139 are indefinite for being in improper Markush format because said claims recite the limitation "a first anchor residue selected from the group consisting of P".

d. Claims 67 and 84 are indefinite because they are incomplete in the omission of essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: there are no steps for preparing a first or a second complex of a motif-bearing peptide fragment and a first or a second HLA molecule.

e. Claims 67, 80, 84, 115 and 139 are indefinite in the recitation of "about 8-11 amino acid residues" because it is not clear how many amino acid residues are actually encompassed by the instant claims.

11. The invention is drawn to an isolated nucleic acid encoding an immunogenic peptide comprising an epitope which comprises a structural supermotif associated with peptide binding to multiple HLA molcules, and pharmaceutical composition thereof. With regard to application of prior art, the filing date of the instant claims is that of the instant application, i.e., 5/30/95, because the scope of the claimed invention is not disclosed in parent application 08/344,824, nor in parent application 08/278,634. The parent application does not support the claimed method; in minimis, the parent application does not disclose a method for making an immunogenic peptide comprising an epitope *consisting of about 8-11 residues* which comprises an *HLA B7 supermotif*, and said parent applications *do not disclose the elected species* APAPAPSWPL.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 67-75, 78-85, 89, 90, 92, 101-116, 120, 121, 123, 132-139, 142-154 and 157-165 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zakut-Houri et al (EMBO J. 4(5), 1985, pages 1251-1255), Harlow et al (Molec. Cell. Biol., 5(7), 1985, pages 1601-1610) Harris et al (Mol Cell Biol., 6(12), 1986, pages 4650-4656) or Lamb et al (Molec. Cell. Biol., 6(5), 1986, pages 1379-1385) each in view of Hill et al (Nature 360(3), 1993, pages 434-439), Huczko et al (J. Immunol., 151(5), 1993, pages 2572-2587, Applicant's IDS reference) and Sette et al (J. Immunol. 153: 5586, 1994).

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al teach the amino acid sequence of the human tumor antigen p53.

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al do not teach a method for making an immunogenic peptide comprising APAPAPSWPL.

Hill et al teach that peptides that are T cell epitopes for HLA-B35 have a position 2 Pro and a Leu at the carboxy terminus. Hill et al teach searching sequences of known antigens for potential epitopes based upon motif amino acids and synthesis of said potential epitopes, e.g., peptides of 8-10 amino acid residues in length (especially column 2 on page 434, last paragraph and Table 2, tr15 and tr20).

Huczko et al teach that peptides that bind to HLA-B7 have Pro at position 2 and L at the carboxy terminus.

Sette et al teach that an affinity threshold of approximately 500 nM (preferably 50nM or less) apparently determines the capacity of a peptide epitope to elicit a CTL response.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have scanned the p53 tumor antigen amino acid sequence of Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al for subsequences such as APAPAPSWPL that possess the motifs, such as those of Hill et al and Huczko et al, for binding to a HLA class I allele expressed in populations of humans, including HLA-B35 and HLA-B7, to have made the said subsequences in a length compatible with binding to HLA class I molecules (i.e., generally 8-11 amino acid residues in length) or in sequences longer than 11 amino acid residues that are capable of being processed to the appropriate size for presentation by class I, to have tested the affinity of the subsequences for affinity of binding to HLA as taught by Sette et al, and to have tested complexes of the peptide/HLA molecules for their ability to be recognized by CTL restricted by said HLA molecules.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce peptides which are potential CTL epitopes for use in vaccines ex vivo or in vivo.

Instant claims 69 and 103 are included because it would have been obvious to prepare and include two antigenic peptide "fragments" in a vaccine in order to make a more effective vaccine. Claims 73, 108, 143 and 161 are included because it would have been obvious to have isolated a peptide from a natural source, i.e., to make said peptide recombinantly. Instant claims 134 and 153 are included because the recitation of the term "less than about 125 nM" renders the claims open to values that are not 125nM.

14. Claims 67-75, 78-85, 89, 90, 92, 101-116, 120, 121, 123, 132-139, 142-154 and 157-165 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zakut-Houri et al (EMBO J. 4(5), 1985, pages 1251-1255), Harlow et al (Molec. Cell. Biol., 5(7), 1985, pages 1601-1610) Harris et al (Mol Cell Biol., 6(12), 1986, pages 4650-4656) or Lamb et al (Molec. Cell. Biol., 6(5), 1986, pages 1379-1385) each in view of Sidney et al (J. Immunol. 154, January 1, 1995, pages 247-259).

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al teach the amino acid sequence of the human tumor antigen p53.

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al do not teach a method for making an immunogenic peptide comprising APAPAPSWPL.

Sidney et al teach peptides with HLA-B7-like supermotif, i.e., Pro at position 2 and hydrophobic/aromatic amino acid residues at the C terminus (especially abstract). Sidney et al teach peptide-based immunizations for the treatment of viral or parasitic infections and cancers and that elicitation of specific class I restricted CTL responses may be crucial in controlling

tumor growth and/or prevention of metastasis (especially paragraph spanning pages 247 and 248). Sidney et al further teach that discovery of peptide epitopes capable of broad cross-reactivity among most or all members of the B7-like supertype family of alleles could be of significant practical importance in the development of peptide-based vaccination strategies (especially last paragraph on page 248 before Materials and Methods section). Sidney et al also teach production of synthetic peptides. Sidney et al teach peptides with affinities less than 500 nM and less than 50 nM, and that good binding is equivalent to an IC50 of less than 500 nM (especially line 8 of column 1 on page 252).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have scanned the tumor antigen p53 amino acid sequence of Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al for subsequences, including APAPAPSWPL, which comprise a binding motif for any of the HLA alleles, including HLA-B*0701, which have the B7-like supermotif of Sidney et al, including Pro at position 2 and Leu at the carboxy terminus, to make the said subsequences in a length compatible with binding to HLA class I molecules (i.e., generally 8-10 or 11 amino acid residues in length) or in sequences longer than 11 amino acid residues that are capable of being processed to the appropriate size for presentation by class I, to complex said subsequences with the class I HLA molecules, to determine affinity, to select peptides with an affinity of less than about 500 nM or 50nM and to test for CTL responses to said peptides when in complex with HLA class I molecules.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to provide peptides for vaccines as taught by Sidney et al.

Instant claims 69 and 103 are included because it would have been obvious to prepare and include two antigenic peptide "fragments" in a vaccine in order to make a more effective vaccine. Claims 73, 108, 143 and 161 are included because it would have been obvious to have isolated a peptide from a natural source, i.e., to make said peptide recombinantly. Instant claims 134 and 153 are included because the recitation of the term "less than about 125 nM" renders the claims open to values that are not 125nM.

15. Claims 67-75, 78-85, 89, 90, 92, 101-116, 120, 121, 123, 132-139, 142-154 and 157-165 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zakut-Houri et al (EMBO J. 4(5), 1985, pages 1251-1255), Harlow et al (Molec. Cell. Biol., 5(7), 1985, pages 1601-1610) Harris et al (Mol Cell Biol., 6(12), 1986, pages 4650-4656) or Lamb et al (Molec. Cell. Biol., 6(5), 1986, pages 1379-1385) each in view of Hill et al (Nature 360(3), 1993, pages 434-439), and Huczko et al (J. Immunol., 151(5), 1993, pages 2572-2587, Applicant's IDS reference)

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al teach the amino acid sequence of the human tumor antigen p53.

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Hill et al teach that peptides that are T cell epitopes for HLA-B35 have a position 2 Pro and a Leu at the carboxy terminus. Hill et al teach searching sequences of known antigens for potential epitopes based upon motif amino acids and synthesis of said potential epitopes, e.g., peptides of 8-10 amino acid residues in length (especially column 2 on page 434, last paragraph and Table 2, tr15 and tr20).

Huczko et al teach that peptides that bind to HLA-B7 have Pro at position 2 and L at the carboxy terminus.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have scanned the p53 tumor antigen amino acid sequence of Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al for subsequences such as APAPAPSWPL that possess the motifs, such as those of Hill et al and Huczko et al, for binding to a HLA class I allele expressed in populations of humans, including HLA-B35 and HLA-B7, to have made the said subsequences in a length compatible with binding to HLA class I molecules (i.e., generally 8-11 amino acid residues in length) or in sequences longer than 11 amino acid residues that are capable of being processed to the appropriate size for presentation by class I, to have selected immunogenic peptides, and to have tested complexes of the peptide/HLA molecules for their ability to be recognized by CTL restricted by said HLA molecules.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce peptides which are potential CTL epitopes for use in vaccines ex vivo or in vivo.

Instant claims 69 and 103 are included because it would have been obvious to prepare and include two antigenic peptide "fragments" in a vaccine in order to make a more effective vaccine. Claims 73, 108, 143 and 161 are included because it would have been obvious to have isolated a peptide from a natural source, i.e., to make said peptide recombinantly. Instant claims 134 and 153 are included because the recitation of the term "less than about 125 nM"

renders the claims open to values that are not 125nM. The claims that recite affinity values are included in the instant rejection because it would have been obvious to have tested and selected for immunogenic peptides as discussed supra, and said immunogenic peptides would have the expected properties of affinity.

16. No claim is allowed.

17. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Marianne DiBrino

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